

# The role of the different Kunitz domains of TFPI in the down-regulation of the extrinsic coagulation pathway

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**Stellingen behorende bij het proefschrift:**

**The role of the different Kunitz domains of TFPI in the down-regulation of the extrinsic coagulation pathway**

1. Although the Kunitz 2 domain of TFPI directly blocks the active site of FXa, the Kunitz 3 and Kunitz 1 domains of TFPI are involved in FXa inhibition by enhancing initial encounter complex formation and isomerization from loose to tight FXa-TFPI inhibitory complex, respectively (this thesis)
2. Protein S stimulates direct inhibition of TF-FVIIa by TFPI (this thesis)
3. Direct inhibition of TF-FVIIa in the absence of FXa, but in the presence of protein S, may be particularly important in patients with elevated plasma TFPI concentrations (this thesis)
4. Low phospholipid concentrations (10  $\mu$ M) are required for optimal stimulation of FXa inhibition by TFPI (this thesis)
5. Rapid inhibition of prothrombinase by TFPI $\alpha$  is mediated through a high affinity exosite interaction between the basic region of TFPI $\alpha$  and an acidic region in FV, which is retained in FXa-activated FVa and platelet FVa (Wood et al., Proc Natl Acad Sci. 2013)
6. Kunitz 1 and Kunitz 2 domains of TFPI bind to active sites of FVIIa and FXa, respectively, simultaneously and immediately after FX is activated by TF-FVIIa (Baugh et al., J Biol Chem. 1998)
7. Plasma levels of TFPI $\alpha$  are reduced in patients with factor V or protein S deficiency (Duckers et al., Blood 2010; Castoldi et al., J Thromb Haemost. 2010)
8. Considering the two-step mechanism of FXa inhibition by TFPI one would predict that TFPI antagonists targeting both the Kunitz 1 and Kunitz 2 domain are more effective TFPI inhibitors than compounds only directed against Kunitz 2 (Valorisation)
9. Many people say that it is the intellect which makes a great scientist. They are wrong: it is character - Albert Einstein
10. Man needs his difficulties because they are necessary to enjoy success - APJ Abdul Kalam
11. When someone shares something of value with you, and you benefit from it, you have a moral obligation to share it with others - Chinese proverb
12. Not all of us can do great things. But we can do small things with great love - Mother Teresa